Published in final edited form as:
Pediatr Blood Cancer. 2005 December ; 45(7): 960–963. doi:10.1002/pbc.20320.

Transient Hyperglycemia in Hispanic Children With Acute Lymphoblastic Leukemia

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Abstract

Background—Transient hyperglycemia occurs commonly during the treatment for childhood acute lymphoblastic leukemia (ALL). The purpose of this study was to examine the incidence of and risk factors for transient hyperglycemia during induction chemotherapy in Hispanic pediatric patients diagnosed with B-Precursor ALL.

Procedure—The study cohort consisted of 155 Hispanic pediatric patients diagnosed with ALL and treated at one of two South Texas pediatric oncology centers between 1993 and 2002. Hyperglycemia was defined as ≥2 glucose determinations of ≥200 mg/dl during the first 28 days of induction chemotherapy.

Results—Overall, 11.0% of the study cohort developed transient hyperglycemia during induction chemotherapy. Age and body mass index (BMI) were both positively associated with the risk of hyperglycemia. Females exhibited a substantially higher risk of hyperglycemia than males, but this association did not reach statistical significance after adjusting for other covariates. Among patients who developed hyperglycemia, 100% of those who required insulin were in the 13–18-year age group and reported a family history of diabetes. Hyperglycemic patients classified as obese (BMI ≥ 95 centile) were more than twice as likely to have required insulin therapy compared to overweight patients (BMI 85–<95 centile) and three times as likely to have required insulin compared to normal weight (BMI <85 centile) patients.

Conclusions—The incidence of chemotherapy-induced transient hyperglycemia in the present study cohort is comparable to that reported in previous pediatric ALL patients. This finding is

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interesting in view of the elevated prevalence of obesity and the underlying dietary behaviors in this Hispanic study cohort.

Keywords

acute lymphoblastic leukemia; children; glucose; obesity

INTRODUCTION

Transient hyperglycemia occurs commonly during the treatment for childhood acute lymphoblastic leukemia (ALL) [1,2]. Early detection and treatment of this condition is critical in preventing diabetic ketoacidosis and hyperosmotic non-ketotic coma [3]. Moreover, patients who develop hyperglycemia during induction chemotherapy may face increased risk of developing complicated infections as well as increased overall mortality and disease recurrence [2]. To date, few studies have assessed the incidence and correlates of chemotherapy-induced hyperglycemia [3]. As previously reported by Pui and colleagues [3], the risk for hyperglycemia is particularly high among children who are obese at the initiation of therapy. Given the high rate of obesity among Hispanic children and adolescents [4,5], Hispanics who are diagnosed and treated for childhood cancer may be at particularly high risk for treatment-related hyperglycemia. The purpose of the present study was to assess the incidence of and risk factors for therapy-induced hyperglycemia in a cohort of predominantly Hispanic children diagnosed with ALL.

PATIENTS AND METHODS

Study Cohort

The study cohort consisted of a consecutive sample of 155 newly diagnosed Hispanic pediatric patients with B-precursor ALL who were diagnosed and treated at CHRISTUS Santa Rosa Children's Hospital (CSRCH), San Antonio, Texas and Driscoll Children's Hospital, Corpus Christi, Texas between January 1, 1993 and December 31, 2002. Because the Centers for Disease Control and Prevention recommends that body mass index (BMI) growth charts be used beginning at 2 years of age when an accurate stature can be determined [6], we excluded all children who were under 2 years at diagnosis. All data were obtained by reviewing existing patient records. Patients were treated primarily on or per Pediatric Oncology Group (POG) legacy protocols (P9000, P9400, and P9900 series) which used the NCI definition for standard or high risk based on the patient's age and white blood cell count (WBC) at diagnosis [7]. Patients received either 3- or 4-drug induction regimen consisting of prednisone or dexamethasone, asparaginase, and vincristine, with or without daunorubicin. The dose schedule for this regimen consisted of prednisone (40 mg/m^2 with a maximum dose of 60 mg) and dexamethasone (6 mg/m^2) for 28 days. Hydration was administered following protocol guidelines with D5W1/2 or D51/4 Normal Saline and bicarbonate (without potassium) at 100–125 ml/m^2/hr.

DATA COLLECTED AND MEASUREMENTS

Clinical data collected at diagnosis included age, gender, ethnicity; pre-existing diagnosis, family history of diabetes, presence of uncontrolled infection, administration of insulin during the induction, WBC, height (cm), and weight (kg). The first glucose level of the morning, fasting before breakfast, was recorded at the following intervals: pre-induction, on day 1–7, 14, 21, and 28 of induction. Hyperglycemia was defined as a plasma glucose concentration of ≥200 mg/dl in two or more determinations during the first 28 days of induction therapy. This definition is consistent with the guidelines of the American Diabetes Association [8] and previous studies of transient hyperglycemia in cancer patients [2,3].

Body surface area (BSA) in square meter (m^2) was determined by the formula: square root of [height (cm) × weight (kg)/3,600] and used to calculate IV fluid rate and extrapolate the amount of glucose infused per hour and minute. BMI was calculated using the formula weight (kg)/height (m) [2]. Age- and gender-standardized BMI z-scores were calculated for each study patient using height, weight, gender, and age data based on the Centers for Disease Control and Prevention (CDC) National Center for Health Statistics (NCHS) growth curves [6]. The z-score indicates the number of standard deviations the measurement is away from the mean for the normal age-sex cohort. Obesity status was defined as a BMI z-score equal or greater than the 95th centile, and overweight status was defined as a BMI z-score ranging from the 85th to less than the 95th centile. BMI is considered the best single weight–height measure in both children and adults with respect to independence of height, correlation with body fat, and prediction of mortality [9,10]. Both definitions are based on the recommendations of an expert panel on childhood obesity [11] and are in accordance with previous studies [4,5,12]. Ethnicity was assigned on the basis of parental report. Age was defined as the patient's age at ALL diagnosis. Family history of diabetes was defined as having a sibling, parent, or grandparent with the clinical diagnosis of type 2 diabetes mellitus, according to the American Diabetes Association criteria, treated with lifestyle modification or pharmacotherapy [8]. This study did not aim to assess the role of type 2 diabetes mellitus in more distant relatives.

STATISTICAL METHODS

The cumulative incidence of hyperglycemia was defined as the percentage of study participants who met the formal criteria for hyperglycemia within each of the study variable subgroups during the 28-day period of induction chemotherapy. BMI centile categories were calculated using the age- and sex-specific standardized BMI z-scores derived from the Centers for Disease Control and Prevention (CDC) National Center for Health Statistics (NCHS) growth curves [6]. Study covariates were defined as follows: age (in months), gender, BMI z-score centile categories (<85th, 85–<95th, ≥95th centiles), family history of diabetes, and ethnicity. The relative risk for each study variable was determined by taking the ratio of probability of developing hyperglycemia in patients with a particular study characteristic compared to those without the characteristic. Adjusted relative risks for each of the study covariates were generated using unconditional multivariate logistic regression (SAS Version 8.2, SAS Institute, Cary, NC).

RESULTS

Seventeen (11.0%) of the 155 patients under study developed transient hyperglycemia during induction chemotherapy (Table I). Females exhibited a higher incidence of hyperglycemia (17.5%) than males (7.1%); patients who were aged 13–18 years at the time of diagnosis had a higher incidence (45.2%) compared to patients who were aged 2–12 years (2.4%); patients with a family history of diabetes had a higher incidence (15.3%) compared to those with no family history of diabetes (7.3%).

Furthermore, transient hyperglycemia increased in a stepwise fashion according to patient BMI. The unadjusted and adjusted relative risks show that the following variables were all positively predictive of transient hyperglycemia: age group 13–18 years (compared to the 2–12 year referent), and both overweight and obesity status (compared to the normal weight references). Female gender was associated with hyperglycemia in the bivariate relative risk assessment, but failed to reach statistical significance after adjusting for the other study covariates. We also conducted the above analyses using two alternative definitions of hyperglycemia: (1) a plasma glucose concentration of ≥200 mg/dl in one or more determinations during the first 28 days of induction; and (2) a concentration of >140 mg/dl

in two or more determinations using the same time frame [8]. The general effect size and statistical significance of the risk ratios yielded in of these analyses were comparable to those described above.

Of the 17 patients who developed hyperglycemia, 8 (47%) were treated with insulin. One hundred percent of hyperglycemic patients who required insulin were in the 13–18-year age group and reported a family history of diabetes. Hyperglycemic patients classified as obese (BMI ≥ 95 centile) were more than twice as likely to have required insulin therapy compared to overweight (BMI 85 to <95%) patients and three times as likely compared to normal weight (BMI <85 centile [13]) patients. The criterion for insulin treatment was variable and could not be uniformly abstracted from patient's records but generally included presentation of diabetes symptoms (e.g., polyuria, polydypsia) and a failure to respond to conventional measures (restriction of fluids with glucose).

DISCUSSION

Transient hyperglycemia occurs commonly in adults and children receiving chemotherapy [1,2]. Pui and colleagues [3] reported hyperglycemia during remission induction in 41 (9.7%) of 421 pediatric patients who received prednisone and L-asparaginase. In their study of 278 adult patients with previously untreated ALL, Weiser and colleagues [2] reported that hyperglycemia occurred in 103 (37%) of patients during induction chemotherapy. Corticosteroids produce insulin resistance, while L-asparaginase reduces glucose-stimulated release of insulin from pancreatic *B*-cells [1]. Most patients who develop therapy-induced hyperglycemia recover when L-asparaginase and glucocorticoids are discontinued, and they suffer no long-term adverse effects [3]. However, careful assessment and prompt treatment of this condition is important in preventing diabetic ketoacidosis and hyperosmotic non-ketotic coma [3]. Treatment includes careful monitoring of serum and urine glucose, diet modification, and increased physical activity [1].

During the induction treatment for ALL, corticosteroids and L-asparaginase exert direct actions on glucose homeostasis [14]. L-asparaginase can directly inhibit insulin release or may indirectly reduced insulin by induction of pancreatitis [15,16]. Normal children and adolescents tolerate glucose infusion rates of up to 5 mg/kg/min (above the highest glucose infusion rate in our study cohort) and maintain euglycemia. Thus, the observed morning glucose level above 200 mg/dl indicates insulin deficiency and/or resistance [17]. Normal glucose homeostasis represents a finely tuned balance between insulin release and action (tissue sensitivity to insulin). Normal β-cells can compensate for defective insulin action by increasing insulin secretion. DeFronzo and colleagues [18] have illustrated a pathogenic sequence of events leading to the development of overt type 2 diabetes. First, predisposed individuals inherit a gene or set of genes that confers insulin resistance and a propensity for B-cell failure. Second, obesity and altered lipid metabolism accentuate those defects. Third, overt diabetic syndrome develops only in those individuals in whom a concomitant insulin secretory defect is also present, regardless of the etiology.

Our finding that 11.0% of patients exhibited transient hyperglycemia, defined as glucose ≥200 mg/dl, in two or more determinations during induction chemotherapy is comparable to the estimate of 9.7% reported by Pui and colleagues in their 1981 study of ALL patients [3]. The similarity in these findings is interesting given the increased rate of overweight status and obesity in our Hispanic study cohort and the national trend of increased overweight status and obesity among children [6]. The prevalence of childhood and adolescent overweight and obesity status has doubled in the past two decades in the US6 and has been particularly high among Hispanics [6]. In our study cohort, 49 (32%) of the 155 study patients were classified as either overweight or obese. By contrast, in their 1981 study, Pui

and colleagues [3] indicate that 4% of their study cohort was obese, defined as a 20% or greater increase over the ideal body weight and height. In assessing the similar incidence rates exhibited by these two study cohorts, it is interesting to note that the present study cohort received chemotherapy agents and doses that were comparable to that of the 1981 study cohort [3]. It will be important for future studies to examine whether such similar incidence rates persist in additional patient cohorts with contrasting ethnic, sociodemographic, and anthropomorphic characteristics.

Our finding that children in the older (>13 years) age group exhibited such a dramatic increase in the incidence of hyperglycemia is particularly interesting. Pui and colleagues [3] reported similar findings, indicating that children aged 10 years and older had an elevated risk of developing therapy-induced hyperglycemia compared to younger aged patients. It is probable that this age effect simply reflects the elevated insulin resistance associated with gonadal steroids during puberty [13,19].

Understanding metabolic complications associated with ALL therapy is an important clinical concern given the recent epidemic rise in obesity rates in the US pediatric population. The prevalence of childhood and adolescent overweight, and obesity status has doubled in the past two decades [6] and has been particularly high among Hispanics [6]. The present study identifies a number of risk factors associated with hyperglycemia during induction chemotherapy for ALL in this predominantly Hispanic study cohort. Given the high risk for development of type 2 diabetes among Hispanic and other minority groups [20], we recommend careful screening for hyperglycemia in the ALL-affected population, and longitudinal assessment for obesity and altered lipid metabolism after induction once remission is achieved. Future investigation of pediatric cohorts diagnosed with cancer is warranted to determine the prognostic impact of transient hyperglycemia for overall long-term survival and progression to metabolic syndrome [21] and overt diabetes.

Acknowledgments

Grant sponsor: National Cancer Institute; Grant number: CA11078.

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TABLE I

Influence of Demographic and Anthropomorphic Characteristics on the Development of Hyperglycemia During Induction Chemotherapy

Study characteristic	Incidence[a] of hyperglycemia	Unadjusted relative risk/95% CI	Adjusted relative risk/95% CI
Overall (n = 155)	11.0	—	—
Gender			
Male (n = 98)	7.1	1.0	1.0
Female (n = 57)	17.5	2.8 (1.0–7.7)	3.8 (0.9–16.2)
Age at baseline			
2–12 years (n = 124)	2.4	1.0	1.0
13–18 years (n = 31)	45.2	33.2 (8.6–127.6)	37.2 (6.1–227.2)
BMI centile			
Normal (n = 106)	2.8	1.0	1.0
Overweight (n = 21)	23.8	3.2 (1.0–10.2)	17.4 (2.5–122.3)
Obese (n = 28)	32.1	7.1 (2.4–20.5)	6.9 (1.2–38.9)
Family history of diabetes			
No (n = 83)	7.3	1.0	1.0
Yes (n = 72)	15.3	2.3 (0.8–6.6)	1.2 (0.3–5.4)

[a]Percentage of patients who developed hyperglycemia during induction chemotherapy.